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CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY OF ORGANOPHOSPHORUS INHIBITORS OF CHOLINESTERASE

- USSR -

/Following is the translation of an article by R. I. Volkova,
N. N. Godovikov, M. I. Kabachnik, L. G. Magazanik, T. A.
Mastryukova, M. Ya. Mikhel'son, Ye. K. Rozhkova, N. K.
Fruyentov and V. A. Yakovlev of the Laboratory of Pharmacology
and Biochemistry of Biologically Active Substances of the
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Academy of Sciences and the Laboratory of Organophosphorus
Compounds of the Institute of Organometallic Compounds of
the USSR Academy of Sciences, Leningrad, in the Russian-
language periodical Voprosy meditsinskoy khimii (Problems
in Medical Chemistry), Vol. VII, No. 3, 1961, pages 250-
258./

We know that the action of nitrogen-containing pharmacologically
active substances on choline receptors and cholinesterases is usually
intensified when the tertiary nitrogen of these compounds is converted
into a quaternary. The same increased activity is observed in a number
of sulfur-containing compounds when the divalent sulfide sulfur is con-
verted into a trivalent sulfonium sulfur. This applies both to cholino-
lytic and cholinomimetic substances and to a like degree to inhibitors
of cholinesterases and their substrates [1]. It has been shown that
we find analogous behavior in organophosphorus compounds which contain
nitrogen [2] and sulfur [1, 3-6]. In particular, we have pronounced.
intensification of physiological activity when we compare the two
compounds GD-7 (O-ethyl-S-beta-ethylmercaptoethylmethylthiophosphinate)
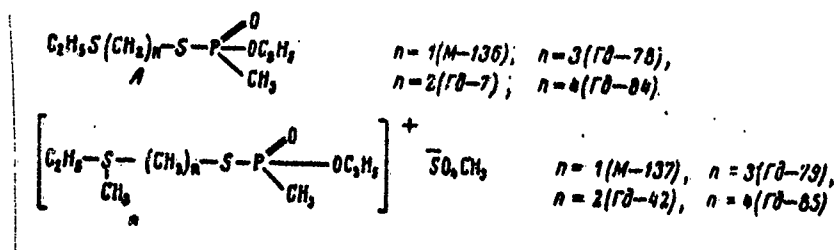and GD-42 (methylsulfomethylate of GD-7) (Cf. Table) [1].

Anticholinesterase Activity of Different Organophosphorus Compounds

$$H_3C-O \diagdown \underset{H_3C \diagup}{P} \diagup^{\displaystyle O} S-(CH_2)_n-R$$

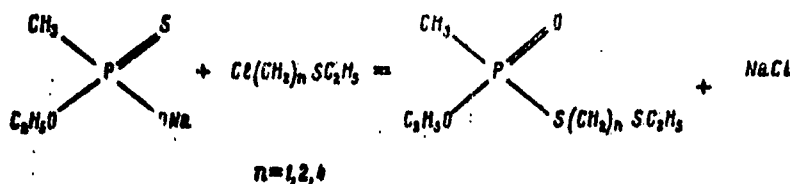| Name	n	R	K II serum cholinesterase liter mol/min	J50 of true cholinesterase (M)	Dosage reducing lability of nerve-mus. synapse in cat (micromol/kg)	Concentration (mole) causing residual contracture of m. rectus abdominis after contraction caused by indirect stimulation	Concentration (mole) causing frog muscle to increase acetylcholine contracture (sensitisation to acetyl-choline).
M-136		$-S-C_2H_5$	$1,20\cdot10^4$	$3,0\cdot10^{-7}$	—	—	0,47	1,4
M-137	1	$-S^+\diagdown^{CH_3}_{C_2H_5}$	$5,00\cdot10^6$ [×415]	$1,0.16\cdot10^{-3}$ [×214]	—	—	—	$0,058$ [×24]
GD-7 Гх-7		$-S-C_3H_5$	$1,98\cdot10^4$	$7,2\cdot10^{-7}$	$1,0\cdot10^{-5}$	$4\cdot10^{-6}$	0,66	4,39
GD-42 Гх-42	2	$-S^+\diagdown^{CH_3}_{C_2H_5}$	$1,80\cdot10^6$ [×90]	$1,0\cdot10^{-3}$ [×720]	$1,0\cdot10^{-3}$ [×6000]	$5\cdot10^{-10}$ [×8000]	$0,007$ [×94]	$0,014$ [×512]
Гх-78		$-S-C_3H_5$	$2,40\cdot10^1$	$9,6\cdot10^{-7}$	$7,0\cdot10^{-5}$	$1\cdot10^{-5}$	0,41	6,2
Гх-79	3	$-S^+\diagdown^{CH_3}_{C_2H_5}$	$4,90\cdot10^5$ [×20]	$3,8\cdot10^{-3}$ [×254]	$4,0\cdot10^{-7}$ [×176]	$6\cdot10^{-8}$ [×166]	$0,011$ [×37]	$0,083$ [×75]
Гх-84		$-S-C_3H_5$	$2,70\cdot10^4$	$4,9\cdot10^{-7}$	$1,3\cdot10^{-5}$	$3\cdot10^{-6}$	0,58	3,9
Гх-85	4	$-S^+\diagdown^{CH_3}_{C_2H_5}$	$1,95\cdot10^3$ [×7]	$6,0\cdot10^{-3}$ [×82]	$5,0\cdot10^{-7}$ [×25]	$1\cdot10^{-7}$ [×39]	$0,065$ [×9]	$0,261$ [×15]

In a study of the reaction with cholinesterase of certain cholinolytic substances with a structure similar to acetylcholine and capable of producing reversible inhibition of cholinesterase (diphacyl, arpenal, pentaphene and other substances and their iodomethylates), we observed that the conversion of tertiary nitrogen into quaternary almost always had an effect on the reaction of the substance with the enzyme. However this effect depends on the position of the nitrogen in the molecule /7/.

If the nitrogen is separated from the ether oxygen by two methyl groups as in acetylcholine proper, methylation produces a much stronger reaction with cholinesterase (methylation of diphacyl – diethylaminoethyl acid). But in the case of methylation of nitrogen separated from the ether oxygen by three methylene groups (arpenal – diethylaminopropyl ester of diphenylacetic acid), we do not have a stronger reaction with the cholinesterase.
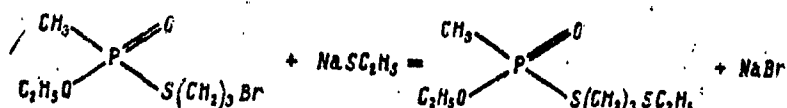
In order to elucidate the effect of the position of the atom carrying a positive charge on the biological activity of organophosphorus compounds we synthesized four O-ethyl-S-ethylmercapto-alkylmethylthiophosphinates (A) and their corresponding methylsulfomethylates (B).
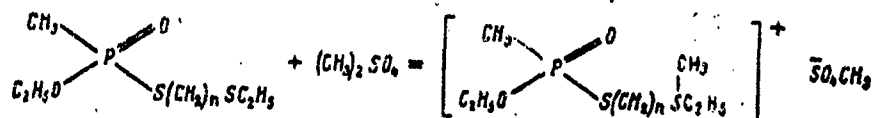
$$C_2H_5S(CH_2)_n-S-P\overset{O}{\underset{CH_3}{\diagdown}}-OC_2H_5$$

A

$$n=1(M-136); \quad n=3(ГД-78);$$
$$n=2(ГД-7); \quad n=4(ГД-84).$$

$$\left[C_2H_5-\underset{\underset{\text{*}}{CH_3}}{S}-(CH_2)_n-S-P\overset{O}{\underset{CH_3}{\diagdown}}-OC_2H_5\right]^{+} \overline{S}O_4CH_3$$

$$n=1(M-137), \quad n=3(ГД-79),$$
$$n=2(ГД-42), \quad n=4(ГД-85)$$

The compounds M-136, GD-7 and GD-84 were synthesized through the action of chlormethylethylsulfide, beta-chlordiethylsulfide and delta-chlorbutylethylsulfide respectively with O-monoethylmethylthiophosphinate sodium.

$$\underset{C_2H_5O}{\overset{CH_3}{\diagdown}}P\underset{ONa}{\overset{S}{\diagup}} + Cl(CH_2)_n SC_2H_5 = \underset{C_2H_5O}{\overset{CH_3}{\diagdown}}P\underset{S(CH_2)_n SC_2H_5}{\overset{O}{\diagup}} + NaCl$$

$$n=1,2,4$$

Compounds GD-78 was synthesized through the reaction of O-ethyl-S-gama-brompropylmethylthiophosphinate and sodium et ylmercaptide.

$$CH_3 \diagdown \!\!\! \overset{\diagup O}{P} \diagdown \!\! S(CH_2)_3 Br \quad + \quad NaSC_2H_5 \quad = \quad CH_3 \diagdown \!\!\! \overset{\diagup O}{P} \diagdown \!\! S(CH_2)_3 SC_2H_5 \quad + \quad NaBr$$

Compounds M-137, GD-42, GD-79 and GD-85 were obtained through the action of dimethylsulfate on the appropriate O-ethyl-S-ethylmercapto-alkylmethylthiophosphinates.

$$CH_3 \diagdown \!\!\! \overset{\diagup O}{P} \diagdown \!\! S(CH_2)_n SC_2H_5 \quad + \quad (CH_3)_2 SO_4 \quad = \quad \left[CH_3 \diagdown \!\!\! \overset{\diagup O}{P} \diagdown \!\! S(CH_2)_n \overset{CH_3}{\underset{}{S}} C_2H_5 \right]^+ \quad \overline{SO_4 CH_3}$$

Synthesis and Analysis: methodology

1. O-ethyl-S-ethylmercaptomethylmethylthiophosphinate (M-136).

To a solution of 6.6g (0.04 mol) of O-monoethylmethylthiophosphinate sodium in 30ml dry acetone we stirred in 6.7g (0.06 mol) of chlormethyl-ethylsulfide /8/. The resulting mixture was heated in a water bath at 60° for 2 hours after which the sodium chloride precipitate was filtered off, the acetone distilled off and the residue sublimated in a vacuum. Production 4.8g of O-ethyl-S-ethylmercaptomethylmethylthiophosphinate (M-136). Yield 55% of theoretical, boiling point 101-101.5° at 4mm Hg, $n^{20}_D 1.5155$, $d^{20}_4 1.559$, MR$_D$ analyzed 56.14, calculated 56.00.

By analysis: C - 33.2 33.4%; H - 7.2 7.1%; P - 14.4 14.6%; S - 29.6 29.5% $C_6H_{15}PS_2O_2$. Calculated C - 33.5%, H - 7.4%; P - 14.9%; S - 29.8%.

2. O-ethyl-S-beta-ethylmercaptoethylmethylthiophosphinate (GD-7).

To sodium ethylate, obtained from 2.3g (0.1 gram atom) sodium and 50ml absolute alcohol, was added 14g (0.1 mol) O-monoethylmethylthiophos-phinate, then slowly at 50° was added 12.4g (0.1 mol) beta-chlordiethyl-

sulfide, mixture boiled in a water bath for 2 hours and the residue
sublimated in a vacuum. Produce 18g of O-ethyl-S-beta-ethylmercapto-
ethyl-methylthiophosphinate (GD-7). Yield 80% of theoretical, boiling
point 98-99° at 1mm Hg, n^{20}_D 1.5181, d^{20}_4 1.1429, MR_D analyzed 60.55,
calculated 60.62.

By analysis: C 37.0%, 36.6%; H 7.5, 7.6%; P 13.5, 13.2%.
$C_7H_{17}PS_2O_2$.

Calculated: C 36.8%; H 7.6%; P 13.5%.

3. O-ethyl-S-delta-ethylmercaptobutylmethylthiophosphinate (GD-84).

Produced by the above method from O-monoethylmethylthiophosphinate
sodium and freshly distilled delta-chlorbutylethylsulfide /Note:
delta-chlorbutylethylsulfide synthesized from delta-oxybutylethyl-
sulfide by reaction with thionyl chloride /9/. Yield 60% of theoretical,
boiling point 74-75° at 6mm Hg, n^{20}_D 1.4895. Very unstable compound.
Data in literature gives boiling point 97-104° at 20mm Hg /10/.
Yield 55% of theoretical, boiling point 126-126.5° at 1mm Hg, n^{20}_D
1.5094, d^{20}_D 1.0970, MR_D analyzed 69.84, calculated 69.86.

By analysis: C 42.0, 42.2%; H 8.2, 8.4%; P 11.6, 11.7%. $C_9H_{21}PS_2O_2$.

Calculated: C 42.1%; H 8.2%; P 12.1%.

4. O-ethyl-S-gamma-brompropylmethylthiophosphinate.

Alcohol solution of O-monoethylmethylthiophosphinate · sodium,
obtained from 28g (0.2 mol) O-monoethylmethylthiophosphinate and 0.2
mol sodium ethylate in 70 ml absolute alcohol, added at 50° to a mixture
of 140g (0.7 mol) 1.3-dibrompropane and 30 ml absolute alcohol.
Resultant mixture boiled in water bath for 2 hours, after which the
separated sodium bromide filtered off, alcohol and excess 1.3-dibrompropane
distilled off and the residue sublimated in a vacuum. Production 27.1g
of)-ethyl-S-gamma-brompropylmethylthiophosphinate. Yield 53% of
theoretical, boiling point 106-107 at 1mm Hg, n^{20}_D 1.5162, d^{20}_D 1.4043,
MR_D analyzed 55.78, calculated 55.73.

By analysis: C 27.7, 27.7%; H 5.6, 5.5%; P 12.2, 12.1%. $C_6H_{14}S_2$
O_2 Br.

Calculated: C 27.6%; H 5.4%; P 11.8%.

5. O-ethyl-S-gamma-ethylmercaptopropylmethylthiophosphinate (GD-78).

To 1.6g (0.07 gram atom) of sodium (divided by Bruhl's method /7/) in 70ml agsolute ether was added 10g (0.16 mol) ethylmercaptan and the mixture stirred until there was total cessation of hydrogen liberation after which 18.2g (0.07 mol) of O-ethyl-S-gamma-brompropylmethylthio-phosphinate was added a drop at a time. Then the mixture was boiled in a water bath for 2 hours, the separated sodium bromide was filtered off, the ether and excess ethylmercaptan distilled off and the residue sublimated in a vacuum. Production was 9.5g of) -ethyl-S-gamma-ethylmercaptopropylmethylthiophosphinate (GD-78). Yield 50% of theoretical, boiling point 112-114° at 2mm Hg, n^{20}_D 1.5121, d^{20}_4 1.1184, MR_D analyzed 65.03, calculated 65.24.

By analysis: C 39.4, 39.4%; H 7.8, 8.0%; P 12.4, 12.4%. $C_8H_{19}PS_2O_2$.

Calculated: C 39.6%; H 7.9%; P 12.8%.

6. Methylsulfomethylate of O-ethyl-S-ethylmercaptomethylmethyl-thiophosphinate (M-137).

1. 6g (0.075 mol) of O-ethyl-S-ethylmercaptomethylmethylthiophos-phinate and 1.0g (0.075 mol) of dimethylsulphate in 3 ml absolute benzene heated for 1 hour in a water bath. Then the benzene was driven off in a vacuum and the remaining syrup twice precipitated from chloroform by ether. After the ether was removed there remained an almost colorless syrupy methylsulfomethylate of O-ethyl-ethylmercaptomethylmethylthio-phosphinate (M-137). Yield 2.2g (close to quantitative).

By analysis: C 27.9, 27.8%; H 3.5, 3.6%; P 8.7, 8.8%. $C_8H_{21}PS_3O_6$.

Calculated C 28.1%; H 3.6%; P 9.1%.

In a similar manner the following compounds provided yields close to quantitative:

7. Methylsulfomethylate of O-ethyl-S-beta-ethylmercaptoethyl-methylthiophosphinate (GD-42), n^{20}_D 1.5210.

By analysis: C 29.2, 29.3%; H 6.5, 6.4%. $C_9H_{23}PS_3O_6$.

Calculated: C 29.2%, H 6.3%.

8. Methylsulfomethylate of O-ethyl-S-gamma-ethylmercaptopropyl-methylthiophosphinate (GD-79), n^{20}_D 1.5169.

By analysis: C 32.5, 32.4%; H 6.7, 6.7%; $C_{10}H_{25}PS_3O_6$.

Calculated: C 32.6%; H 6.8%.

9. Methylsulfomethylate of O-ethyl-S-delta-ethylmercaptobutyl-methylthiophosphinate (GD-85), n^{20}_D 1.5138.

By analysis: C 34.6, 34.7%; H 7.1, 7.2%; P 8.0, 7.9%. $C_{11}H_{27}PS_3O_6$.

Calculated: C 34.8%; H 7.1%; P 8.1%.

Anticholinesterase activity with relation to pseudocholinesterase was tested by two methods. For purified horse serum (preparation purified 40 times) we determined the constants (K_{II}) of inhibition rate at pH 7 and 40° (second of the two methods described in an article by R. I. Volkova and V. A. Yakovlev, 1959 [11]) in the absence of acetylcholine and with concentrations of the organophosphorus compound and cholinesterase close to stoichiometric.

For raw horse serum we determined J_{50} - the concentration of the organophosphorus compound which reduces cholinesterase activity by 50%.

For true cholinesterase of defibrinated cow's blood we determined only J_{50}. Following conditions observed in making determinations. To 1ml blood we added 2 ml water or an inhibitor solution. After 10-12 mins of preliminary contact between the blood and the inhibitor acetylcholine chloride was added (1 ml $1 \cdot 10^{-3}$). After 2 minutes the reaction between the cholinesterase and the acetylcholine was stopped by the addition of trichloracetic acid. The amount of acetylcholine remaining undecomposed was determined by Hestrin's method [12]. The entire experiment was performed in a controlled water chamber at 38°.

The pharmacological effect was rated on the basis of the effect of the preparation on the transverse and smooth musculature of animals. The effect on tonic muscle fibers was studied on an isolated m. rectus abdominis of a frog. We determined the concentrations of the organophosphorus compounds capable of doubling the tonic contraction caused by acetylcholine and the concentrations which induce residual contraction with stimulation from the nerve.

In evaluating the effect on the nontoxic muscles of warm-blooded animals we determined the minimum doses which intensify the passimal reaction of the gastrocnemius of a cat (urethane anesthesia) with high frequency stimulation of a peripheral segment of the sciatic nerve /13/.

In order to evaluate the effect on the smooth muscles we determined the minimal dose which injected intravenously caused total spasm of the bronchial musculature. The Concett-Ressler-Turpayev method was used /14,15/.

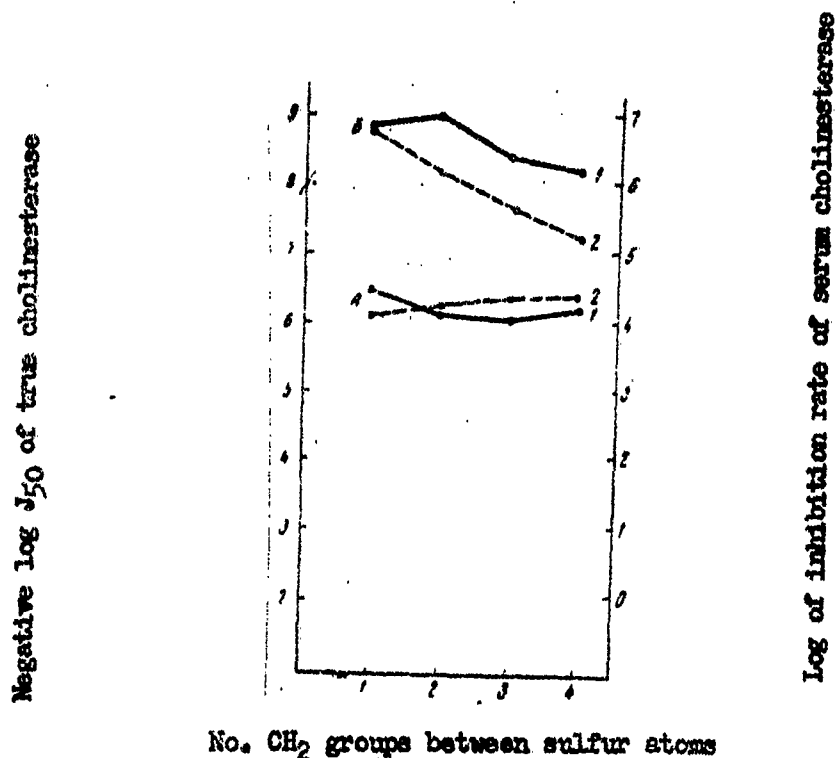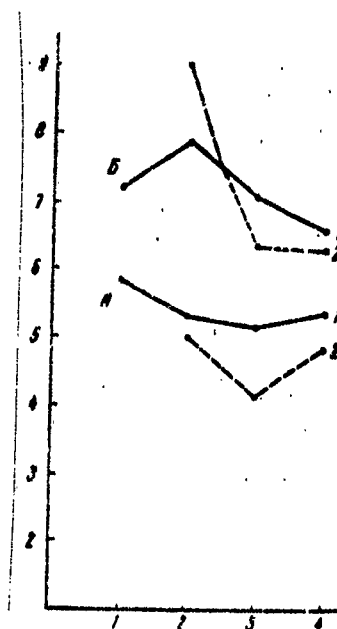No. CH$_2$ groups between sulfur atoms

Fig. 1 Anticholinesterase action of the organophosphorus compounds studied.
1 - true cholinesterase; 2 - serum cholinesterase;
A - indicators of substances with a sulfide atom of sulfur;
B - with a sulfonium atom.

- 8 -

Negative log of effective concentrations and doses
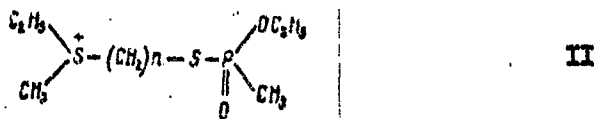
No. CH$_2$ groups between sulfur atoms

Fig. 2 Pharmacological activity of the substances studied.
1 - dose (in mol/kg) causing total bronchial spasm in a cat; 2 -
concentration (in mol) causing residual contracture of m.
rectus abdominis of a frog. Other symbols same as in Fig. 1

Research Results

All the data on the biological effects of organophosphorus compounds are summarized in the table. In Fig. 1 we have a graphic representation of results of determining the anticholinesterase activity, in Fig. 2 the pharmacological effect.

$$H_5C_2 - S - (CH_2)_n - S - P \Big\langle^{OC_2H_5}_{CH_3} \qquad\qquad I$$
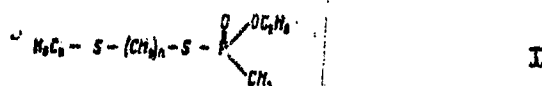
From the table we can see that in series of compounds (I) there are no real or regular changes in biological activity when the number of methylene groups n changes from 1 to 4. All four preparations possess similar and comparatively low biological activity. All the corresponding sulfonium compounds (II) are much more active.

$$^{C_2H_5}_{CH_3}\!\!\Big\rangle \overset{+}{S} - (CH_2)n - S - P \Big\langle^{OC_2H_5}_{CH_3}\quad\underset{O}{\overset{\|}{}} \qquad\qquad II$$

Most important is the fact that quantitatively the increase in activity with the appearance of a positive charge changes abruptly depending on the number of methylene groups between the sulfonium and the ether atoms of sulfur. When there are one or two methylene groups methylation intensifies activity hundreds or even thousands of times (compare preparations M-136 and M-137, GD-7 and GD-42). When there are three methylene groups in between the increase is less pronounced (GD-78 and GD-79). With four groups the intensification is minimal (GD-84 and GD-85).

With respect to constants of rate of inhibition of cholinesterase activity the maximal increase was observed with a separation of a single methylene group (M-136 and M-137). In determining the J_{50} of true cholinesterase and the dosage inducing bronchial spasm, we found the maximal increase in activity when two methylene groups intervene (GD-7 and GD-42). It is possible that this is related to the extreme instability of the sulfonium compound with a single methylene group. Constants of inhibition rate were determined in other cases but in determining two types of biological activity the rapid hydrolysis of the preparation in a water medium may distort results toward lower activity or render determination completely impossible.

In the main pharmocological effects varied parallel to the change in anticholinesterase activity. This agrees with the concept that the pharmacological activity of the organophosphorus compounds under study is based on their ability to inhibit cholinesterase. Qualitatively the changes were always the same: both the anticholinesterase and pharmacological activity increased with methylation. Quantitative differences may depend on the fact that the pharmacological activity is effected by such factors as the rate of development of the inhibitory effect, the ability of the organophosphorus compounds to activate or inactivate in the body (hydrolysis), their capacity for reacting not only with cholinesterase but other enzymes and protein bodies, the distribution of the organophosphorus compound in the body, their greater or lesser ability to stimulate (nonanticholinesterase activity) the choline receptors directly, etc.

Particularly indicative in this respect are the results of experiments on an isolated m. rectus abdominis of a frog. The survival conditions of the isolated organ were reduced to a minimum and thus reduced the effect of many of the above mentioned side factors. Yet it was this object which produced the most striking results. With two methylene groups between the sulfur atoms a preparation of the sulfonium type - GD-42 - was 8000-10000 times stronger than its analog with divalent sulfur (GD-7). With three methylene groups the increase was only 166-175 times (GD-78 and GD-79). With four methylene groups (Cf. table) between the sulfur atoms the appearance of sulfonium sulfur increased activity only 26-30 times (GD-84 and GD-85).

Mechanism of Activity Increase As A Function of Onium Grouping

The question of the importance of the free positive charge and its position in the organophosphorus molecule for the biological activity must be discussed on the basis of modern concepts of the chemical reaction between cholinesterase and acetylcholine and organophosphorus compounds [16-22].

Two hypotheses are possible in the light of these concepts.

1. The constant positive charge assures the establishment of an ion bond between the cation center of the substance and the anion point of the enzyme and thus orients the phosphorus organic molecule with relation to the active surface of the cholinesterase, facilitating the reaction of the ester grouping of the substance and the esterase point of the enzyme.

2. The positive charge has an induction effect on the thio-
ether grouping of the organophosphorus compound, increasing the
effective positive charge on the phosphorus atom and thus facilitating
the reaction with the enzyme.

Both of these effects must facilitate the phosphorylation of
the cholinesterase.

It is probably true that both factors play a part in the reaction
of acetylcholine and cholinesterase.
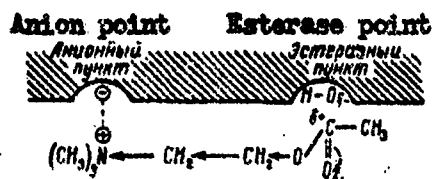
A. The orienting effect of the positive charge must be maximal
in the sulfonium organophosphorus compound in which the distance
between the sulfonium sulfur and the phosphorus is closest to the
distance between the quaternary nitrogen and the carbonyl carbon in
the acetylcholine molecule (a) while a reduction in this distance
(b) or an increase (c) must weaken the anticholinesterase action.
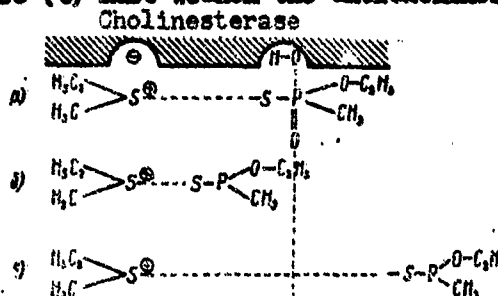
In cases b and c the formation of an ion bond between the
sulfonium sulfur and the anion point of the enzyme facilitates to a
lesser degree (than in a) the reaction of the ester grouping of the
organophosphorus compound with the esterase point of the enzyme.

The strongest anticholinesterase effect and the greatest degree
of increase in methylation were observed in a compound with a single
methylene group. Calculations show that for a compound with a single
methylene group the distance between the sulfur and phosphorus ($4.6A^{\circ}$)
is nearest to the distance between the ammonium nitrogen and the
carbonyl carbon in acetylcholine ($4.7A^{\circ}$).
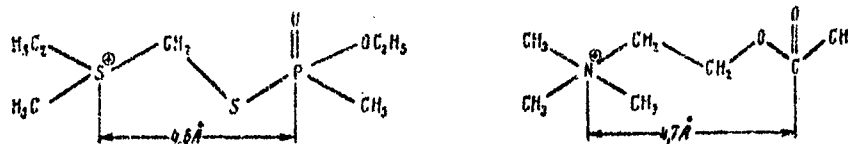
Thus the recurrent weakening of the effect of the charge in the organophosphorus compounds studied as the number of methylene groups increased from 1 to 4 agree very well with the hypothesis that the importance of the charge lies in its effect in orientation.

B. Induction effect. Let us now consider another possible explanation for the increase in activity when the charge appears on the sulfur atom. The cation center developing in the molecule has an induction effect, i.e., it induces a shift in the electron cloud along the atom chain and activates the ester portion of the molecule, facilitating the nucleophilic attack from the esterase point of the enzyme and increasing the mobility of the P-S bond which is disrupted in phosphorylation of the enzyme.
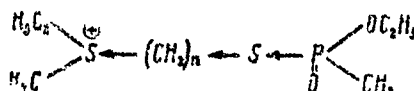
If this is so, we might expect that in an organophosphorus compound of a sulfonium structure there is an increase in reactive capacity not only toward the cholinesterase but toward water as well since the reaction of an organophosphorus compound with water and hydroxyl ions in analogous in mechanism to the reaction of the organophosphorus compound with the esterase point of cholinesterase /16/. Of course the orientation influence is not of importance in the reaction with water.

The kinetics of the hydrolysis of sulfonium organophosphorus compounds was studied in an alkaline medium at 22° by potentiometric titration. Values of logarithms of bimolecular constants of the rate of reaction of organophosphorus compounds with CH⁻ are compared with constants of the reaction rate of cholinesterase of blood serum in

Fig. 3. We can see that the reaction capacity of sulfonium organophosphorus compounds with regard to OH- ions increases regularly with a decrease in the distance between the cation center of the molecule and the phosphoryl group. This increase occurs concomitantly with the increase in anticholinesterase activity. The greatest anticholinesterase activity
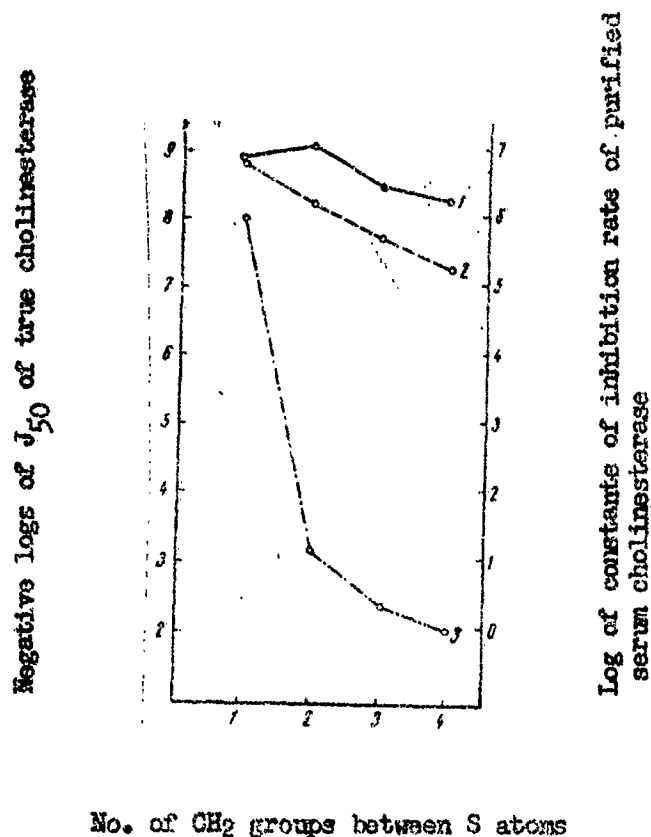

No. of CH_2 groups between S atoms

Fig. 3. Anticholinesterase activity and alkaline hydrolysis of sulfonium organophosphorus compounds.

1 - true cholinesterase; 2 - purified serum cholinesterase; 3 - alkaline hydrolysis of organophosphorus compounds (non-logarithmic scale). Other designations same as in Figs. 1 and 2.

is found in that preparation (with one methylene group) which is the most rapidly hydrolyzed. As the number of methylene groups between the sulfur atoms increases both anticholinesterase activity and hydrolysis become weaker. These facts agree very well with the hypothesis that the mechanism of activity increase in organophosphorus compounds as related to the sulfonium sulfur in the molecule is an induction effect which grows weaker as the chain grows longer.

The results obtained may be interpreted as deriving from the hypothesis of the importance of the orientation effect of the onium center in the phosphorus organic compound molecular as well as from the hypothesis that the decisive role is played by the induction effect produced by the onium center on the ester group of the organophosphorus molecule.

It is still difficult to decide which effect is the more important since the structure with a single methylene group was most advantageous for both the orientation and the induction effect: as the number of methylene groups increases there is a concomitant weakening of both effects along with biological activity. A quantitative evaluation of both proposed mechanisms will be the subject of future investigations.

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